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TITLE: Value of MRI and DTI as Biomarkers for Classifying Acute Spinal Cord Injury

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14. ABSTRACT

The purpose of this study is to determine if diffusion tensor imaging (DTI) in conjunction with conventional magnetic resonance imaging (MRI) can reliably forecast neurologic recovery after spinal cord injury (SCI).

As of the time of the original report (10/29/12) there were 7 patients enrolled in the study. Twenty patients with no neurologic deficit and were screened with conventional MRI and DTI have been identified and the images have been collected. No imaging data have been analyzed to date.

15. SUBJECT TERMS
None provided.

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Introduction

Use of MRI/DTI may improve accuracy in stratifying SCI patients that are being selected for clinical trials to test novel therapies. Trials which utilize MRI/DTI at the point of entry have the potential to demonstrate therapeutic efficacy with fewer patients. The objective of our proposal is to prove that the MRI features of SCI and DTI when used in conjunction with the initial neurologic assessment will provide a better method to classify patients during their initial hospitalization and will better discriminate patients that have capacity for spontaneous functional recovery from those with no inherent capacity for recovery. The results derived from this project have the capacity to radically alter the methods by which we categorize SCI at the point of entry into the healthcare system by more accurately characterizing the extent of their injuries and providing the opportunity to administer appropriate therapies in the critical few hours after injury. This has direct benefit to the individual patient and their families in gauging expectations for recovery and in selecting patients for novel therapies. The goal of this study is to combine the information obtained from the physical examination of the SCI patient at the time of injury with the anatomic and physiologic information provided through MRI and DTI to better predict which patients might realize the most benefit from a new medication. If the added value of MRI and DTI improves the pre-selection process of patients for a new medication, this could also provide a secondary benefit in helping to expedite the drug approval process by decreasing the number of patients required to prove that the drug actually benefits patients.

In this study, 80 SCI patients and 20 controls will be assessed with the standard neurological clinical exam at enrollment and be imaged at one time point with MRI and DTI. The SCI patients will then be followed over 6 months with serial motor and sensory evaluations performed at fixed time points. MRI, DTI, and clinical variables will be analyzed to determine which combination provides most accurate prediction of clinical outcome at 6 months.

Body

Task 1. Obtain human subjects approval

Competed 07/27/11, as reported in the Year 1 annual report, by month 10 (instead of month 4). Preparation of the protocol, the TJU IRB submission and submission to the DoD were completed by month 2. DoD queries returned by month 5 and responses delivered to DoD in same week. We were finally given permission to begin open enrollment on 7/27/2011 (month 10).

Task 2. Enrollment of patients

2a. Identify 80 patients with isolated cervical injuries admitted to the Thomas Jefferson University Hospital Level 1 Regional Resource Trauma Center and Regional Spinal Cord Injury Center

There have been a total of 7 patients enrolled in the study as of October 29th, 2012, with 5 subjects being enrolled since the previous report. The most significant challenge for this year has been patient recruitment. Vagaries of the regional referral patterns have shifted a considerable number of potential patients outside of our referral network which has substantially limited the number of patients that could be considered for enrollment. Nevertheless we have managed to enroll the majority of patients who meet inclusion criteria over the past year.

Table 1: Patient demographics and follow-up information

Pt ID	Sex	Race	Age	Other Information (as of 04/26/13)
TJUH-001	F	Black	27	Completed all follow-up
TJUH-002	M	Cauc	70	Patient expired due to underlying causes before 3 month follow up
TJUH-003	M	Cauc	37	Completed all follow-up
TJUH-004	F	Cauc	72	Refused 6 month follow up
TJUH-005	M	Cauc	66	Refused 6 month follow up
TJUH-006	M	Cauc	62	Lost to follow up prior to 2 week f/u for colon cancer
TJUH-007	M	Cauc	67	24 hour and 2 week not done

2b. Identify 20 trauma patients with no neurologic deficit who are being screened with MRI for ligamentous injury

We have successfully identified twenty trauma patients with no neurologic deficit who have been screened with MRI.

2c. Assess inclusion / exclusion criteria

Inclusion/exclusion criteria have been reviewed and have been met for all enrolled patients.

2d. Review study with potential patient and obtain informed consent

The study protocol has been reviewed with all eligible patients and 7 patients have been enrolled in the study as of 10/29/12.

Task 3. Perform one conventional MR exam with additional DTI sequences within 12 hours of presentation on all 100 subjects

3a. Four scans in the sagittal and axial planes: T1 and T2 weighted spin-echo sagittal sequences, gradient echo sagittal sequence, relative T2* weighted sequence

Imaging has been obtained on the 7 enrolled SCI patients, as well as the 20 controls.

3b. Additional non-cardiac gated, DTI acquisition sequence

Additional non-cardiac gated DTI has been obtained on the 7 enrolled SCI patients, as well as the 20 controls.

Task 4. Perform clinical neurological assessments on 80 SCI study patients

4a. Upon enrollment evaluate ASIA impairment grade and assess neurological level of injury

Table 2: Enrollment ASIA score, level of injury, and ASIA pin/touch scores at time points

Pt ID	Injury Level	Initial ASIA	24 hour	72 hour	2 week	3 month	6 month
TJUH-001	C5	D	108/102	91/84	80/99	88/86	95/96
TJUH-002	C6	B	59/60	n/a	42/49	n/a	n/a
TJUH-003	C8	B	31/72	29/78	33/77	80/80	47/101
TJUH-004	C4	B	24/34	16/22	n/a	45/57	n/a
TJUH-005	C1	D	n/a	45/33	39/79	96/96	n/a
TJUH-006	C4	C	16/34	37/65	n/a	n/a	n/a
TJUH-007	C2	D	n/a	56/112	n/a	111/110	112/112

4b. Assess recovery of upper (SCIM) and lower (SCIM and WISCI-II) extremity muscles.
Currently, SCIM data on all patients is being collected, however WISCI-II was not collected.

4c. Calculate MIS for the upper and lower extremities

Table 3: MIS scores at time points (upper/lower) and recovery rate (Lucas and Ducker)

Pt ID	24 hour	72 hour	2 week	3 month	6 month	Recovery rate
TJUH-001	37/32	38/37	42/44	47/48	50/50	1/1
TJUH-002	8/0	n/a	12/8	n/a	n/a	.095/.16
TJUH-003	48/0	46/0	48/0	50/0	50/0	1/.18
TJUH-004	4/7	1/0	0/4	16/7	n/a	.260/0
TJUH-005	n/a	26/36	28/39	incompl/45	n/a	.08/.64
TJUH-006	0/3	0/11	n/a	n/a	n/a	0/.17
TJUH-007	n/a	34/45	n/a	49/50	48/50	.875/1

4d. Calculate MIS recovery rate using the method of Lucas and Ducker
See Table 3.

4e. Calculate the number of muscles with minimally useful function from MIS scores

Table 4: Number of muscles with minimally useful function (upper/lower)

Pt ID	24 hour	72 hour	2 week	3 month	6 month
TJUH-001	5/8	8/8	10/10	10/10	10/10
TJUH-002	2/0	n/a	2/0	n/a	n/a
TJUH-003	10/0	10/0	10/0	10/0	10/2
TJUH-004	0/0	0/0	0/0	0/0	n/a
TJUH-005	n/a	6/8	6/8	incompl/10	n/a
TJUH-006	0/0	3/1	n/a	n/a	n/a
TJUH-007	n/a	8/10	n/a	10/10	10/10

Task 5. Conventional MR image evaluation by two independent neuroradiologists

5a. Determine length and location of the spinal cord lesion on mid-sagittal images
Images will be evaluated once 30 patients have been enrolled.

5b. Assess morphology (edema and hemorrhage) using three characteristics seen on MRI: (1) cord swelling, (2) cord edema, and (3) acute cord hemorrhage (deoxyhemoglobin)
Images will be evaluated once 30 patients have been enrolled.

5c. Measure length of edema and hemorrhage
Images will be evaluated once 30 patients have been enrolled.

Task 6. DTI image analysis
6a. Transfer DTI data to an independent workstation for post-processing
For the six completed SCI patients (as of 10/26/12) and the 20 patients without neurologic injury, the data was transferred to a workstation for custom post-processing.

6b. Perform image co-registration and white matter threshold
An automated co-registration algorithm was implemented to preferentially filter for preserved white matter fibers in each axial section.

6c. Calculate whole cord FA, MD, LD ($\lambda 1$) and TD ($\lambda 23$) for each of the contiguous slice location and create DTI feature anatomic maps (months 4-34)
Slice by slice FA, MD, LD and TD were calculated for each contiguous axial slice covering the entire cervical spinal cord.

6d. Calculate proportion of individual axial DTI slices that deviate from normal controls
Comparative and group analysis is deferred pending more patient accrual.

Task 7. Data analysis and report preparation
Once 30 patients are enrolled, interim data analysis will be performed.

Key Research Accomplishments

- Developed a validated, reproducible DTI protocol that request less than five minutes of acquisition time.
- Trained an entire pool of MR technologists to perform the protocol autonomously.
- Developed a data management plan to transfer raw data to the analysis platform.
- Developed an automated quality control process to rapidly process the DTI data to assess for flaw/errors which might prohibit patient enrollment.
- Developed an enrollment strategy with the rehabilitation co-investigators to ensure capture of all potential patient candidates that meet inclusion criteria.
- Continued to refine the DTI protocol as needed to minimize distortion and statistical variability.
- Are now utilizing two distinct methods to analyze DTI data to better understand variations contributed by algorithms.
- Continued to collective normative DTI data for age-matched controls.

Reportable Outcomes

None to date on the current patients.

Conclusion

We are behind on SCI patient enrollment principally due to idiosyncratic changes in referral patterns to our Level I trauma and SCI center. We have managed to capture the majority of potential patients that meet our entry criteria. Research team has continued to focus on novel methods to analyze existing DTI datasets to take advantage of the time by testing, re-testing and refining our imaging protocol and analytical tools on retrospective clinical data to ensure that our acquisition methodology and analytical tools are sound.

Reference

Not applicable

Appendices

None.

Supporting Data

Not applicable